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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/852,165	05/08/2001	Peter Lind	00231regUS/PHRM-0442	3975

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EXAMINER	
LANDSMAN, ROBERT S	

ART UNIT	PAPER NUMBER
1647	14

DATE MAILED: 04/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/852,165	LIND ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-79* is/are pending in the application.

4a) Of the above claim(s) *1-29 and 36-79* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-35* is/are rejected.

7)☒ Claim(s) *30-35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,6,9,11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Comparisons A-D* .

DETAILED ACTION

1. Formal Matters

A. The Information Disclosure Statement, filed 8/14/01, has been entered into the record.

B. The Supplemental Information Disclosure Statement, filed 1/02/02, has been entered into the record.

C. The Supplemental Information Disclosure Statement, filed 8/19/02, has been entered into the record.

D. The Supplemental Information Disclosure Statement, filed 9/3/02, has been entered into the record.

E. Claims 1-179 are pending and were subject to restriction in Paper No. 10, dated 9/3/02. In Paper No. 13, filed 10/3/02, Applicants elected Group III, claims 30-35, with traverse and argue that no serious burden would be imposed upon the Examiner by combining several groups. However, as recited in the Restriction requirement mailed 9/3/02, the Groups comprise non-overlapping subject matter and a search of one group would not necessarily overlap a search of any other group. Furthermore, Applicants did not state which groups should be combined. However, if the claims of Group III are allowable, method claims which are commensurate in scope with this Group may be allowable if no issues are raised under 35 USC 112. This restriction is deemed proper and is, therefore, made FINAL.

2. Information Disclosure Statement

A. Reference FO on the Form PTO-1449 filed 1/2/02, has been lined through since an International Search Report is not a proper citation for an IDS.

3. Specification

A. The title is objected to since it is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. In addition, the word "novel" should be removed since all patents claim novel subject matter.

The following title is suggested: Polypeptides encoding G protein-coupled receptors.

4. Claim Objections

A. Claims 30-35 are objected to since claim 30, from which claims 31-35 depend, depend from non-elected claim 1.

5. Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

A. Claims 30-35 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility. These claims are directed to a polypeptide of SEQ ID NO:2, or variations thereof. However, the invention encompassed by these claims has no apparent or disclosed patentable utility. This rejection is consistent with the current utility guidelines, published 1/5/01, 66 FR 1092. The instant application has provided a description of an isolated protein. However, the instant application does not disclose a specific and substantial biological role of this protein or its significance.

However, it is clear from the instant specification that the claimed receptor is what is termed an "orphan receptor" in the art. The instant application does not disclose the biological role of the claimed protein or its significance. Applicants disclose in the specification that the claimed receptor is believed to be a G protein-coupled receptor. However, the basis that the receptor of the present invention is a 7 transmembrane receptor is not predictive of a use. There is little doubt that, after complete characterization, this protein will probably be found to have a patentable utility. This further characterization, however, is part of the act of invention and, until it has been undertaken, Applicants' claimed invention is incomplete.

The instant situation is directly analogous to that of which was addressed in Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. 101, which required that an invention must have either an immediate obvious or fully disclosed "real-world" utility. The court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility," "[u]nless and until a process is refined and developed to this point - where specific benefit exists in currently available form – there is insufficient justification for permitting an applicant to engross what may prove to be a broad field," and "a patent is not a hunting license," "[i]t is not a reward for the search, but compensation for its successful conclusion."

The specification discloses that the polypeptid6s of the invention is similar to G protein-coupled receptors. Based on the structural similarity, the specification asserts that the newly disclosed SEQ ID NO:2 is also a G protein-coupled receptor. However, this assertion cannot be accepted in the absence of supporting evidence, because generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases.

For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene.

Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan the

utility of the claimed polypeptide of SEQ ID NO:2 which is only known to be homologous to G protein-coupled receptors. Therefore, the instant claims are drawn to a polynucleotide encoding a protein which has a yet undetermined function or biological significance. There is no actual and specific significance which can be attributed to said protein identified in the specification. For this reason, the instant invention is incomplete. In the absence of a knowledge of the natural ligands or biological significance of this protein, there is no immediately obvious patentable use for it. To employ a protein of the instant invention in the identification of substances which bind to and/or mediate activity of the said receptor is clearly to use it as the object of further research which has been determined by the courts to be a non-patentable utility. Since the instant specification does not disclose a "real-world" use for said protein then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. 101 as being useful.

Furthermore, since the polypeptide of the invention is not supported by a specific and substantial asserted utility or a well established utility, the polynucleotide encoding this protein, as well as any variants or fragments of the claimed polypeptide also lack utility.

6. Claim Rejections - 35 USC § 112, first paragraph - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. Claims 30-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to use the instant invention. Specifically, since the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

B. Furthermore, even if the claims possessed utility under 35 USC 101, claims 30-35 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while then being enabling for the protein of SEQ ID NO:2, does not reasonably provide enablement for proteins which are "homologous to," "or allelic variants of" SEQ ID NO:2, or which comprise "at least one conservative amino acid substitution" of SEQ ID NO:2. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

First, the breadth of the claims is excessive with regard to claiming all proteins which are "**homologous**" to, or "**allelic variants**" of SEQ ID NO:2, or which comprise "**at least one conservative amino acid substitution**" of SEQ ID NO:2. These proteins would comprise one or more amino acid substitutions, deletions, insertions and/or additions to the protein of SEQ ID NO:2. In addition, as recited in claim 1, from which claims 30-35 ultimately depend, nucleic acid molecules encoding "**at least a portion**" of nGPCR-2067 proteins would comprise one or more nucleic acid substitutions, deletions, insertions and/or additions to SEQ ID NO:1. Similarly, proteins encoded by these portions would also comprise one or more amino acid substitutions, deletions, insertions and/or additions to the protein of SEQ ID NO:2.

Applicants provide no guidance or working examples of proteins other than that of SEQ ID NO:2, nor do they provide a *function* of these proteins. Applicants have provided no guidance as to what critical residues are required to maintain the functional characteristics of the protein of SEQ ID NO:2, nor is it predictable to one of ordinary skill in the art how to make a functional protein which is less than 100% identical to that of SEQ ID NO:2. Regarding claim 33, the entire protein can be altered with conservative amino acid substitutions and, regarding claims 32 and 33, Applicants have not provided a specific functional limitation as well as any % identity to limit the amount and types of substitutions which can occur to the protein of SEQ ID NO:2. For example, and without adding new matter, if the protein of the present invention were known to be a mu opioid receptor, the claims should recite "wherein the protein is at least 95% identical to SEQ ID NO:2 and wherein said protein binds morphine" (or has some other mu-specific activity.

Furthermore, claims 34 and 35 include in scope allelic variants of the disclosed protein. The Examiner was not able to find a definition of "allelic variant," but notes that the implied definition is at odds with the art accepted meaning of allelic variant, since the definition of "allele" is drawn exclusively to the state of a gene itself, and has no direct connotation regarding the protein encoded by the gene (it is noted that even genes or sequences which do not encode protein may exist as alleles). For example, Ayala

and Kiger (Modern Genetics, Benjamin/Cumings 1980) define allele as "One of two or more alternative forms of a gene, each possessing a unique nucleotide sequence; different alleles of a given gene are usually recognized, however, by the phenotypes rather than by comparison of their nucleotide sequences." Thus, while allelic genes may result in a phenotypic change, the word does not have any particular connotation as to the encoded protein. Given this, the Examiner cannot determine how one would distinguish, merely by examination of the protein, whether a protein were the result of expression of a different allele, or alternatively, were merely one of a number of ultimate species that might be obtained by the expression of one of the two sequences particularly disclosed in this application. In addition, enablement is not commensurate in scope with claims to proteins encoded by allelic variants of the disclosed sequences. Even if the specification disclosed that the claimed proteins are useful for their biological activity, allelic variants often encode proteins with quantitatively or qualitatively altered or absent biological activity. Therefore, the specification does not teach how to use such variants, nor is adequate guidance provided for the skilled artisan to predict, *a priori*, which variants would reasonably be expected to retain biological function.

Therefore, in summary, the breadth of the claims is excessive with regard to Applicants claiming all proteins which are "**homologous**" to, or "**allelic variants**" of SEQ ID NO:2, or which comprise "**at least one conservative amino acid substitution**" or "**a portion**" of SEQ ID NO:2. Applicants provide no guidance or working examples of these proteins, or variants thereof, nor is it predictable to the artisan how to make a functional protein other than SEQ ID NO:2. Therefore, the Examiner holds that undue experimentation is required to practice the claimed invention.

7. Claim Rejections - 35 USC § 112, first paragraph – written description

A. Claims 30-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These are genus claims. Proteins which are "**homologous**" to SEQ ID NO:2 would have one or more amino acid substitutions, deletions, insertions and/or additions to SEQ ID NO:2. In addition, as recited in claim 1, from which claims 30-35 ultimately depend, nucleic acid molecules encoding "**at least a portion**" of nGPCR-2067 proteins would comprise one or more nucleic acid substitutions, deletions, insertions and/or additions to SEQ ID NO:1. Similarly, proteins encoded by these portions would also

comprise one or more amino acid substitutions, deletions, insertions and/or additions to the protein of SEQ ID NO:2

The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. Thus the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claims do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the nucleic acid or protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO:2, alone is insufficient to describe the genus. One of skill in the art would reasonable conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus at the time the invention was made.

B. Claims 34 and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO:2 and, therefore, the written description is not commensurate in scope with the claims drawn to allelic variants of SEQ ID NO:2.

The specification does not provide any particular definition for the term '**allele**.' In this circumstance, the meaning of the term is the ordinary usage in the art. The ordinary meaning of the term 'allele' is one of two or more alternate forms of a gene occupying the same locus in a particular chromosome or linkage structure and differing from other alleles of the locus at one or more mutational sites. See, Rieger et al., *Glossary of Genetics* (1991), p. 16. The Rieger et al. reference discloses that there are at least seven different kinds of alleles in addition to the 'strictly neutral' type discussed above for claims 26-29. See Rieger, pp 16-17 (amorphs, hypomorphs, hypermorphs, antimorphs, neomorphs, isoalleles and unstable alleles). The alleles are distinguished by the effect their different structures have on phenotype. According to Rieger et al., alleles may differ functionally according to their distinct structures. For example, they may differ in the amount of biological activity the protein product may have, in the amount of protein produced, and/or the kind of activity the protein product will have.

Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of

SEQ ID NO:2, and its encoding DNA of SEQ ID NO:1, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides (or, more importantly, the intended polypeptide of the claims) and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

The specification only discloses that SEQ ID NO:1 encodes SEQ ID NO:2. The specification proposes to discover other members of the genus by using a hybridization procedure. There is no description of the mutational sites that exist in nature, and there is no description of how the structure of the DNA encoding the claimed "allelic variants" relates to the structure of different alleles. In addition, according to the standard definition, the genus includes members that would be expected to have widely divergent functional properties. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele is representative of other unknown alleles having concordant or discordant functions. The common attributes of the genus are not described and the identifying attributes of individual alleles, other than SEQ ID NO:1 (or the protein of SEQ ID NO:2), are not described. The nature of alleles is that they are variant structures where the structure of one does not provide guidance to the structure and function of others. According to these facts, one of skill in the art would conclude that the Applicant was not in possession of the claimed genus because a description of only one member of the genus is not representative of the variants of the genus and is insufficient to support the claim.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Furthermore, In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus

is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention."

Therefore only an isolated DNA molecule comprising a DNA sequence consisting of SEQ ID NO:1 and equivalent degenerative codon sequences thereof, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

8. Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

A. Claims 30-32 are rejected under 35 U.S.C. 102(e) as being anticipated by Behan et al. (US Patent No. 6,204,017). The claims recite a polypeptide encoded by a nucleic acid molecule wherein said polypeptide is homologous to SEQ ID NO:2, said nucleic acid molecule encoding at least a portion of nGPCR-2067, or that the protein encodes SEQ ID NO:2. Behan et al. teach a protein which is 100% identical to SEQ ID NO:2 of the present invention (Sequence Comparison A) and its encoding nucleic acid molecule (Sequence Comparison B).

B. Claims 30, 32 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Goodearl (US Patent No. 5,882,893). The claims recite a polypeptide encoded by a nucleic acid molecule wherein said polypeptide is homologous to SEQ ID NO:2, said nucleic acid molecule encoding at least a portion of nGPCR-2067. The claims also recite that the homologous polypeptide has at least one conservative amino acid substitution. Goodearl teaches a polypeptide which is 35.8% homologous to SEQ ID NO:2 and which comprises at least one conservative amino acid substitution (Sequence Comparison C). Goodearl also teaches the nucleic acid encoding this homologous polypeptide (Sequence Comparison D).

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
April 28, 2003

ROBERT LANDSMAN
PATENT EXAMINER